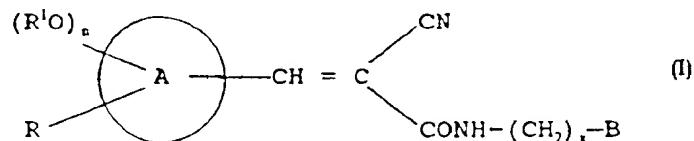




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(71) Applicant (for all designated States except US): PHARMACIA S.P.A. [IT/IT], Via Robert Koch, 1,2, I-20152 Milan (IT).			
(72) Inventors; and			
(73) Inventors/Applicants (for US only): BUZZETTI, Franco [IT/IT], Via della Gallarana, 4, I-20052 Monza (IT). CRUGNOLA, Angelo [IT/IT], Viz Ruggiero Settimo, 30, I-21100 Varese (IT). LONGO, Antonio [IT/IT], Via Porpora, 160, I-20131 Milan (IT). BRASCA, Gabriella, Maria [IT/IT], Via Dante Alighieri, 15, I-20090 Cusago (IT). BALLINARI, Dario [IT/IT], Via C. Jannozzi, 8, I-20097 S. Donato Milanese (IT).			
(74) Common Representative: PHARMACIA S.P.A.; Patent and Documentation Dept., Via Bisceglie, 104, I-20152 Milan (IT).			

(54) Title: SUBSTITUTED BETA-ARYL AND BETA-HETEROARYL-ALPHA-CYANOACRYLAMIDE DERIVATIVES AS TYROSINE KINASE INHIBITORS



(57) Abstract

The present invention relates to new compounds of formula (I), wherein A is a bicyclic ring chosen from naphthalene, tetrahydronaphthalene, quinoline, isoquinoline and indole; B is an R² substituted benzene ring or an unsubstituted pyridine or thiophene ring; R is hydrogen, C₁-C₆ alkyl, halogen, nitro, cyano, carboxy or a group NR³R⁴, wherein each of R³ and R⁴ is independently hydrogen or C₁-C₆ alkyl; R¹ is hydrogen, C₁-C₆ alkyl or C₁-C₆ alkanoyl; R² is hydrogen, C₁-C₆ alkyl, halogen, nitro, cyano, carboxy, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkanoyloxy or a group NR³R⁴, wherein R³ and R⁴ are as defined above; n is zero or an integer of 1 to 2; x is zero or an integer of 1 to 5; and the pharmaceutically acceptable salts thereof. The compounds of the invention are useful as tyrosine kinase inhibitors.

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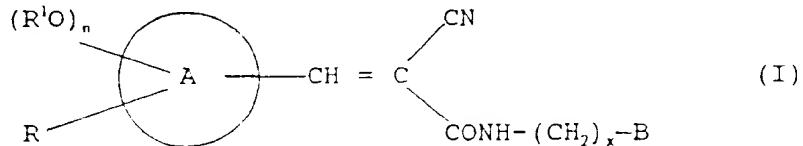
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SUBSTITUTED BETA-ARYL AND BETA-HETEROARYL-ALPHA-CYANOACRYLAMIDE DERIVATIVES AS TYROSINE KINASE INHIBITORS

The present invention relates to new N-substituted β -aryl-
 5 and β -heteroaryl- α -cyanoacrylamide derivatives to a process
 for their preparation, to pharmaceutical compositions
 containing them and to their use as therapeutic agents.

The present invention provides compounds having the
 following general formula (I)

10



wherein

15 A is a bicyclic ring chosen from naphthalene, tetrahydronaphthalene, quinoline, isoquinoline and indole;
 B is a R^2 substituted benzene ring or an unsubstituted pyridine or thiophene ring;

20 R is hydrogen, C_1-C_6 alkyl, halogen, nitro, cyano, carboxy or a group NR^3R^4 wherein each of R^3 and R^4 is independently hydrogen or C_1-C_6 alkyl;

25 R^1 is hydrogen, C_1-C_6 alkyl or C_1-C_6 alkanoyl;

R^2 is hydrogen, C_1-C_6 alkyl, halogen, nitro, cyano, carboxy, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkanoyloxy, or a group NR^3R^4 wherein R^3 and R^4 are as defined above;

n is zero or an integer of 1 to 2;

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x is zero or an integer of 1 to 5;
and the pharmaceutically acceptable salts thereof.

In the compounds of formula (I) when A is naphthalene, quinoline, isoquinoline or indole, then each of the substituents R and OR' may be independently on either of the two rings constituting the bicyclic system, when A is tetrahydronaphthalene whilst they are only on the benzene ring of the bicyclic system.

When n is 2, the OR' groups may be the same or different.

10 The invention includes within its scope all the possible isomers, stereoisomers, in particular Z and E isomers and their mixtures, and the metabolites and the metabolic precursors or bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

15 The alkyl groups and the alkyl moieties in the alkoxy, alkanoyl or alkanoyloxy groups may be branched or straight alkyl chains.

A C₁-C₆ alkyl is preferably a C₁-C₄ alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl or tert-butyl, in particular methyl or ethyl.

A C₁-C₆ alkoxy group is preferably a C₁-C₃ alkoxy, in particular methoxy.

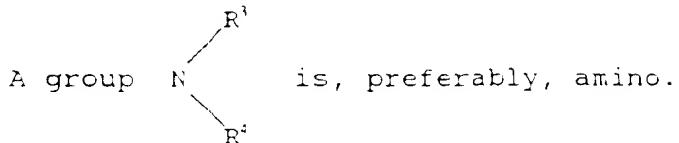
A C_1 - C_6 alkanoyl group is preferably a C_2 - C_3 alkanoyl group, in particular acetyl or propionyl.

25 A C₁-C₆ alkanoyloxy group is preferably a C₂-C₃ alkanoyloxy group, in particular acetyloxy or propionyloxy.

A halogen is preferably fluorine, chlorine or bromine, in

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particular fluorine or chlorine.



5 Under tetrahydronaphthalene more precisely we intend
5,6,7,8-tetrahydronaphthalene.

When A is naphthalene the R and R'O substituents and the acrylamide side chain are preferably on the same benzene moiety.

10 When A is 5,6,7,8-tetrahydronaphthalene the R and R'O substituent and the acrylamide side chain are preferably on the aromatic benzene moiety.

When A is quinoline the acrylamide side chain is preferably attached to the 4- or 5-position of the quinoline ring and the R and R¹O substituents are preferably on the same aryl or heteroaryl moiety of said ring.

When A is isoquinoline the acrylamide side chain is preferably attached to the 3 or 5-position of the isoquinoline ring and the R and R'O substituents are preferably on the benzene moiety of said ring.

When A is indole ring the acrylamide side chain is preferably attached to the pyrrole moiety and the R and R'0 substituents are preferably on the benzene moiety of said ring. In this case preferably A is a 3-indolyl group.

25 Of course only one of the substituents R, R'0 and
acrylamide side chain can be linked to the same carbon of
the A ring.

The R^2 substituent is preferably in para position on the

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benzene ring.

When one of R and R² is NO₂, COOH or NR³R⁴, then the other has preferably a different meaning.

Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts, with inorganic acids, e.g. hydrochloric, sulphuric, perchloric and phosphoric acid, or organic acids, e.g. acetic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acid, and salts with inorganic bases, e.g. sodium, potassium, calcium or magnesium base, or with organic bases, e.g. alkylamines, preferably triethylamine.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above, but which nevertheless upon administration to human being are converted directly or indirectly in vivo into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I), wherein

A is tetrahydronaphthalene, quinoline, isoquinoline and indole;

B is R² substituted benzene or unsubstituted pyridine;

R is hydrogen or halogen with the exception of indole derivatives where R can also be carboxy or amino;

R¹ is hydrogen or methyl;

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R² is hydrogen, halogen, cyano, hydroxy, carboxy or amino;

n is 0, 1 or 2 and

x is 0, 1, 2 or 3;

5 and the pharmaceutically acceptable salts thereof.

A particularly preferred class of compounds of the invention are the compounds of formula (I) in which

A is tetrahydronaphthalene, quinoline, isoquinoline and indole;

10 B is R² substituted benzene or an unsubstituted pyridine;

R is hydrogen with the exception of indole derivatives where R can also be carboxy or amino;

R¹ is hydrogen or methyl;

15 R² is hydrogen or hydroxy;

n is 0, 1 or 2; and

x is 0, 1 or 2;

and the pharmaceutically acceptable salts thereof.

More preferably the OR¹ substituents are linked to position
20 3 and 4 when A is 5,6,7,8-tetrahydronaphth-1-yl and to position 4 when A is 5,6,7,8-tetrahydronaphth-2-yl. When A is quinoline the OR¹ substituent is more preferably linked to position 8. When A is indole the R or OR¹ substituent is more preferably linked to position 5. In all above
25 mentioned cases the R² substituent is more preferably linked to position 4'.

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Examples of specific compounds of the invention are the following compounds, which, may be either Z- or E- isomers or Z,E-mixtures of said isomers:

N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

5 N-(4'-hydroxyphenyl)- β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-phenyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

10 N-(4'-hydroxyphenyl) β -(3,4-dihydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-benzyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

15 N-(4'-hydroxybenzyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-benzyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

20 N-(4'-hydroxybenzyl) β -(3,4-dihydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-phenethyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

N-(4'-hydroxyphenethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-phenethyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-
25 yl)- α -cyanoacrylamide;

N-(4'-hydroxyphenethyl) β -(3,4-dihydroxy-5,6,7,8-tetra-
hydronaphth-1-yl)- α -cyanoacrylamide;

N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -

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cyanoacrylamide;

N-(4'-hydroxyphenyl) β -(4-hydroxy-5,6,7,8-tetrahydro-

naphth-2-yl)- α -cyanoacrylamide;

N-benzyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -

5 cyanoacrylamide;

N-(4'-hydroxybenzyl) β -(4-hydroxy-5,6,7,8-tetrahydro-

naphth-2-yl)- α -cyanoacrylamide;

N-phenethyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)-

α -cyanoacrylamide;

10 N-(4'-hydroxyphenethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-

naphth-2-yl)- α -cyanoacrylamide;

N-phenyl β -(4-quinolyl)- α -cyanoacrylamide;

N-(4'-hydroxyphenyl) β -(4-quinolyl)- α -cyanoacrylamide;

N-benzyl β -(4-quinolyl)- α -cyanoacrylamide;

15 N-(4'-hydroxybenzyl) β -(4-quinolyl)- α -cyanoacrylamide;

N-phenethyl β -(4-quinolyl)- α -cyanoacrylamide;

N-(4'-hydroxyphenethyl) β -(4-quinolyl)- α -cyanoacrylamide;

N-phenyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;

N-(4'-hydroxyphenyl) β -(8-hydroxy-5-quinolyl)- α -cyano-

20 acrylamide;

N-benzyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;

N-(4'-hydroxybenzyl) β -(8-hydroxy-5-quinolyl)- α -cyano-

acrylamide;

N-phenethyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;

25 N-(4'-hydroxyphenethyl) β -(8-hydroxy-5-quinolyl)- α -

cyanoacrylamide;

N-phenyl β -(3-isoquinolyl)- α -cyanoacrylamide;

N-(4'-hydroxyphenyl) β -(3-isoquinolyl)- α -cyanoacrylamide;

- ω -

N-benzyl β -(3-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(3-isoquinolyl)- α -cyanoacrylamide;
N-phenethyl β -(3-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(3-isoquinolyl)- α -cyano-
5 acrylamide;
N-phenyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4-hydroxyphenyl) β -(5-isoquinolyl)- α -cyanoacrylamide;
N-benzyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(5-isoquinolyl)- α -cyanoacrylamide;
10 N-phenethyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(5-isoquinolyl)- α -cyano-
acrylamide;
N-phenyl β -(3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(3-indolyl)- α -cyanoacrylamide;
15 N-phenethyl β -(3-indolyl)- α -cyanoacrylamide;
N-phenyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
20 N-phenyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-phenyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
25 N-benzyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(3-indolyl)- α -cyanoacrylamide;
30 N-(4'-hydroxyphenyl) β -(5-hydroxy-3-indolyl)- α -cyano-

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acrylamide;

N-(4'-hydroxybenzyl) β -(5-hydroxy-3-indolyl)- α -cyano-

acrylamide;

N-(4'-hydroxyphenethyl) β -(5-hydroxy-3-indolyl)- α -cyano-

5 acrylamide;

N-(4'-hydroxyphenyl) β -(5-carboxy-3-indolyl)- α -cyano-

acrylamide;

N-(4'-hydroxybenzyl) β -(5-carboxy-3-indolyl)- α -cyano-

acrylamide;

10 N-(4'-hydroxyphenethyl) β -(5-carboxy-3-indolyl)- α -cyano-

acrylamide;

N-(4'-hydroxyphenethyl) β -(5-amino-3-indolyl)- α -cyanoacryl-

amide;

N-(4'-hydroxybenzyl) β -(5-amino-3-indolyl)- α -cyanoacryl-

15 amide;

N-(4'-hydroxyphenethyl) β -(5-amino-3-indolyl)- α -cyano-

acrylamide;

N-phenyl β -(5-methoxy-3-indolyl)- α -cyanoacrylamide;

N-benzyl β -(5-methoxy-3-indolyl)- α -cyanoacrylamide;

20 N-(3-pyridyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

N-(3-pyridyl) β -(3-indolyl)- α -cyanoacrylamide;

N-(3-pyridyl) β -(5-methoxy-3-indolyl)- α -cyanoacrylamide;

N-(3-pyridyl) β -(4-quinolyl)- α -cyanoacrylamide;

25 N-(3-pyridylmethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

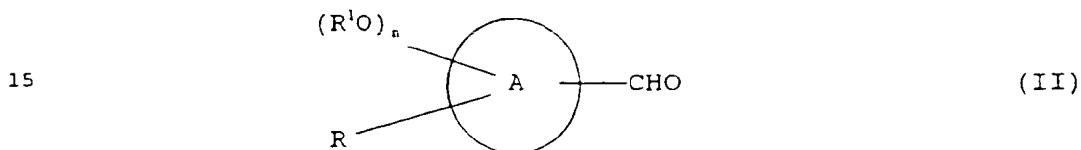
N-(3-pyridylmethyl) β -(3-indolyl)- α -cyanoacrylamide;

N-(3-pyridylmethyl) β -(5-methoxy-3-indolyl)- α -cyano-

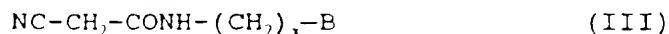
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acrylamide;
N-(3-pyridylmethyl) β -(4-quinolyl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;
5 N-(2-pyridylmethyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(5-methoxy-3-indolyl)- α -cyano-acrylamide;
N-(2-pyridylmethyl) β -(4-quinolyl)- α -cyanoacrylamide,
and, when appropriate, the pharmaceutically acceptable
10 salts thereof.

The compounds of the invention, and the pharmaceutically acceptable salts thereof, can be obtained by a process comprising the condensation of an aldehyde of formula (II)



wherein A, R, R' and n are as defined above, with a compound of formula (III)



20 wherein R² and x are as defined above, and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt

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thereof, and/or, if desired, converting a salt into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I) into the single isomers.

5 Each of the substituents R, R¹O and -CHO in a compound of formula (II) may be independently on either of the rings in naphthalene, quinoline, isoquinoline and indole, whilst in the case of tetrahydronaphthalene they are preferably on the same aromatic ring.

10 The condensation of a compound of formula (II) with a compound of formula (III) may be carried out according to known methods as herebelow described. For example it may be carried out under the conditions of the Knoevenagel reaction as described, e.g., by G. Jones in Organic 15 Reactions 15, 204 (1967).

Suitable catalysts are organic bases such as pyridine, piperidine or diethylamine. The condensation may be performed in an inert organic solvent, e.g., pyridine, ethanol; methanol, benzene or dioxane at temperatures 20 ranging from about 0°C to about 100°C. Preferably the reaction is carried out in hot ethanol solution in the presence of piperidine catalyst.

A compound of formula (I) can be converted into another compound of formula (I) according to known methods. For 25 example the de-etherification of a compound of formula (I) wherein R¹O is methoxy, so as to obtain a compound of

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formula (I) wherein R¹O is hydroxy, can be carried out for example with boron tribromide as described by J.F.N. McOmie in *Tetrahedron* 24, 2289 (1968). The reaction may be performed in an inert organic solvent such as dichloromethane or benzene under an inert atmosphere (e.g. nitrogen) at temperatures ranging from about -78°C to about room temperature.

The conversion of a compound of formula (I) in which R or R² is nitro into the corresponding compound of formula (I), 10 wherein R or R² is amino, may be carried out following known methods, for example with a variety of reducing agents, e.g. sodium sulfide in hydroalcoholic solution, metallic iron with ammonium chloride in aqueous solvent, or for instance, catalytic hydrogenation using e.g. palladium 15 charcoal catalyst at low hydrogen pressure in an inert organic solvent.

The alkylation of a compound of formula (I), wherein R¹O or R² is hydroxy, so as to obtain the corresponding compound of formula (I), wherein R¹O or R² is C₁-C₆ alkoxy, may be 20 obtained, e.g., by reaction with sodium hydride and C₁-C₆ alkyl iodide in a high boiling aromatic solvent such as xylene.

The acylation of a compound of formula (I), wherein R² or R¹O is hydroxy, in order to obtain the corresponding 25 compound of formula (I), wherein R² or R¹O is a C₁-C₆

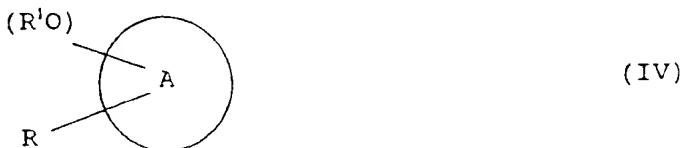
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alkanoyloxy, can be performed, e.g., by reaction with a suitable carboxylic acid anhydride in the presence of a basic agent at temperatures ranging from room temperature to reflux temperatures.

5 The optional salification of a compound of formula (I) as well as the conversion of a salt into a free compound, and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods. For example the separation of a mixture of geometric isomers, 10 e.g., cis- and trans-isomers, may be carried out by fractional crystallization from a suitable solvent or by chromatography, either column chromatography or HPLC.

The compounds of formula (II) may be obtained according to known methods from compounds of formula (IV)

15



wherein A, R and R' are as defined above.

For example when compound (IV) contains phenolic groups, 20 i.e. R'O is hydroxy, the well known Reimer-Tiemann method can be applied. Thus the phenolic compound is treated with chloroform and alkali hydroxides in an aqueous or hydroalcoholic solution. Another useful method for the synthesis of aromatic or phenolic aldehydes has been

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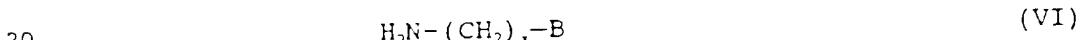
described by H. Gross et al. in *Chem. Ber.* 96, 308 (1963). Accordingly a compound of formula (IV), in which the OR¹ group may be present or not, can be treated with a dichloromethyl ether, e.g. dichloromethyl methyl ether, in 5 the presence of a Friedel-Crafts catalyst such as titanium tetrachloride or aluminium trichloride in an inert solvent like dichloromethane or nitrobenzene at temperatures ranging from about 0°C to about 60°C.

3-Formylindole derivatives of formula (II) can be obtained 10 for example from compounds of formula (IV) by formylation with N-methylformanilide and phosphorus oxychloride according to the well known Vilsmeier-Haack method [for a review see W.G. Jackson et al. in *J. Am. Chem. Soc.* 103, 533 (1981)].

15 The compounds of formula (III) may be obtained by known methods from a compound of formula (V)



wherein R⁵ is a C₁-C₆ alkyl group, in particular a methyl group, by condensation with a compound of formula (VI)



wherein R² and x are as defined above.

Preferably the condensation is carried out by heating equimolar amounts of compound (VI) and compound (V) in the

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form of its methylester at temperatures ranging from about 100°C to 200°C for several hours without adding a solvent.

Alternatively a compound of formula (III) can be obtained by reacting a compound of formula (V) wherein R⁵ is H with 5 a compound of formula (VI) wherein B and X are as defined above using dicyclohexylcarbodiimide as coupling agent and conducting the reaction in an inert solvent such as THF or benzene at temperatures ranging from room to reflux temperatures.

10 The compounds of formulae (IV), (V) and (VI) are known or can be obtained by known methods.

When in the compounds of formula (I) and in the intermediate products thereof groups are present which need to be protected before submitting them to hereabove 15 illustrated reactions, they may be protected before the reaction take place and then deprotected at the end of the reaction, according to well known methods in organic chemistry.

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PHARMACOLOGY

The compounds of the invention possess specific tyrosine kinase inhibiting activity. It is believed that tyrosine kinase inhibitors may be of great importance in the control 5 of uncontrolled cellular reproduction, i.e. in cellular reproduction disorders. Hence the compounds according to the present invention can be useful in the treatment of pathological proliferation disorders in mammals, including humans. They can be useful e.g. in the treatment of benign 10 and malign tumors. They are able to cause tumor regression and to prevent tumor metastasis and the growth of micrometastasis.

Moreover they can also be useful for the treatment of leukemia and psoriasis. They have also utility in the 15 control of immune system diseases (immunosuppressants), angiogenesis and atherosclerosis (atheromatous plaque) as far as protein kinases are involved in these diseases.

Recent studies on the molecular basis of neoplastic transformation have identified a family of genes, designed 20 oncogenes, whose aberrant expression causes tumorigenesis. For example, the RNA tumor viruses possess such an oncogene sequence whose expression determines neoplastic conversion of infected cells. Several of their oncogene-encoded proteins, such as pp60^{v-src}, p70^{ras}, p130^{egr-1} and p70^{egr-2} 25 display protein tyrosine kinase activity, that is they catalyze the transfer of the γ -phosphate from adenosine triphosphate (ATP) to tyrosine residues in protein substrate. In normal cells, several growth factor

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receptors, for example the receptors for PDGF, EGF, α -TGF and insulin, display tyrosine kinase activity.

Binding of the growth factor (GF) activates the receptor tyrosine kinase to undergo autophosphorylation and to phosphorylate closely adjacent molecules on tyrosine.

Therefore, it is thought that the phosphorylation of these tyrosine kinase receptors plays an important role in signal transduction and that the principal function of tyrosine kinase activity in normal cells is to regulate cell growth.

10 Perturbation of this activity by oncogenic tyrosine kinases
that are either overproduced and/or display altered
substrate specificity may cause loss of growth control
and/or neoplastic transformation. Accordingly, a specific
inhibitor of tyrosine kinases can be useful in
15 investigating the mechanism of carcinogenesis, cell
proliferation and differentiation and it can be effective
in prevention and chemotherapy of cancer and other
pathological proliferative conditions.

In particular the compounds of the invention can be used in
20 the treatment of cancers, metastasis, leukemia, psoriasis,
angiogenesis, atherosclerosis (atheromatous plaque) and
immune system diseases as far as protein kinases are
involved in these diseases.

25 The tyrosine specific protein kinase activity of the
compounds of the invention is shown, e.g., by the fact that
they are active in the in-vitro and in-vivo test described
herebelow.

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In-vitro Assay

p45 v-abl Kinase Purification

The enzyme used in our test was the p45 v-abl tyrosine kinase which represents the catalytic domain of the Abelson tyrosine kinase (isolated from the Abelson murine leukemia virus). The p45 v-abl kinase was produced and isolated as described by Wang et al. in J. Biol. Chem. 260, 64 (1985) and by Ferguson et al. in J. Biol. Chem. 260, 3652 (1985) and in Biochem. J. 257, 321 (1989).

10 p45 v-abl Kinase Assay

(Val⁵)-Angiotensin II phosphorylation was performed by incubation with 40 ng of purified abl-kinase and ($\gamma^{32}\text{P}$)-ATP, in 50 μl of buffer containing Tris-HCl 25 mM, pH 8.0, MgCl₂, 10 mM and dithiothreitol 0.1 mM (kinase buffer). The 15 reaction mixture was incubated for the indicated time at 30°C and the reaction stopped by adding 50 μl of 5% trichloroacetic acid. After a brief incubation on ice, tubes were centrifuged. The supernatants were spotted on phosphocellulose paper squares (Whatman P-81) and washed 20 extensively in acetic acid. The radioactivity bound to dried phosphocellulose squares was measured in a liquid scintillation counter. IC₅₀ values were calculated from triplicate determinations of each experimental point. Each inhibitor was tested at concentrations ranging from 0 to 25 400 μg in the presence of fixed concentrations of peptide (2 mM) and ATP (50 μM).

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In-vivo Assay

K562 Cell Growth Inhibition Assay

K562 cells, a human myelogenous leukemia cell line, were seeded into a 24 wells tissue culture plate (Falcon 3047) (10000/well) in the presence of increasing concentrations of the compounds. After 72 h, cells were harvested and were counted using a cell counter (Coulter Counter - ZM). The percent of inhibition was evaluated in respect to the untreated control cells.

10 The inhibitory activity data for a representative compound according to the present invention, obtained both in the in-vitro p45 v-abl kinase assay and in the in-vivo human chronic myeloid leukemia K562 cell growth inhibition assay described above, are set out in Table 1.

15 Table I Inhibition of p45 v-abl kinase and K562 cell
growth

		IC ₅₀ (μM)
N-phenyl β -(8-hydroxy-5-quinolyl)-	<u>y-abl</u>	<u>K562</u>
2-oxo-1,2-dihydro-3H-1,4-dioxolo[3,2-b]pyrrolidine-3-carboxamide	3.4	0.66

In view of their high activity and low toxicity, the compounds of the invention can be used safely in medicine.

For example, the approximate acute toxicity (LD_{50}) of the

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compounds of the invention in the mouse, determined by single administration of increasing doses and measured on the seventh day after the treatment was found to be negligible.

5 The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions, rectally, in the form of suppositories; parenterally, e.g. intramuscularly, or by 10 intravenous injection or infusion; or topically.

The dosage depends on the age, weight, condition of the patient and administration route; for example, the dosage adopted for oral administration to adult humans may range from about 10 to about 150-200 mg per dose, from 1 to 5 15 times daily. Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

The invention includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient, which can be a carrier or 20 diluent.

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable 25 form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose,

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dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, 5 methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate, effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, 10 non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating or film-coating processes.

15 The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspensions.

The syrup may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

20 The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethyl-cellulose or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections 25 may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine

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hydrochloride.

The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile, aqueous, 5 isotonic saline solutions.

The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

10 Compositions for topical application, e.g. creams, lotions, or pastes, can be prepared by admixing the active ingredient with a conventional oleaginous or emulsifying excipient.

A further object of the present invention is a combined 15 method of treatment of cancer in mammals, including humans, in need of such treatment, said method comprising administering

- 1) a compound of formula (I), or a pharmaceutically acceptable salt thereof, and
- 20 2) an additional antitumor agent, in amounts and close enough together in time sufficient to produce a therapeutically useful effect.

Object of the present invention is also to provide products containing a compound of formula (I), or a pharmaceutically 25 acceptable salt, and an additional antitumor agent as a combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

The term "antitumor agent" is meant to comprise both a

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single antitumor drug and "cocktails" i.e. a mixture of such drugs, according to the clinical practice.

Antitumor agents that can be formulated with a compound of the invention or alternatively, can be administered in a 5 combined method of treatment, are e.g. doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastin and mitomycin or a mixture of two or more thereof.

10 The compounds of the invention can therefore be used in a treatment to ameliorate a cancer pathology. They may be administered to a patient suffering from a cancer treatable with an antitumor agent, for example an anthracycline glycoside such as doxorubicin, daunomycin, epirubicin or 15 idarubicin as mentioned above, together with the antitumor agent.

A compound of the invention and an antitumor agent such as an anthracycline glycoside can be administered to improve the condition of a patient having a leukaemia such as 20 myeloblastic leukaemia, lymphoma, sarcoma, neuroblastoma, Wilm's tumor or malignant neoplasm of the bladder, breast, lung or thyroid.

The following examples illustrate but do not limit the invention.

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Example 1

N-phenyl β -(δ -hydroxy-5-quinolyl)- α -cyanoacrylamide

A solution of δ -hydroxy-5-quinolincarboxaldehyde (1.732 g, 0.010 mol), N-phenyl cyanoacetamide (1.602 g, 0.010 mol) and piperidine (0.255 g, 0.003 mol) in absolute ethanol (50 ml) was heated for 3 h at reflux. The reaction mixture was chilled to about 10-15°C, the precipitate filtered, the residue washed with ice-cooled ethanol and dried under vacuum. Almost pure title compound was obtained in about 10 75% yield (2.365 g).

Compounds of high purity are obtained by crystallization from ethanol.

$C_{19}H_{13}N_3O_2$ calculated: C 72.37 H 4.15 N 13.33

found: C 72.40 H 4.20 N 13.30

15 MS m/z 315.

IR cm^{-1} : 3300-3600 (NH,OH), 2210 (CN), 1680, 1600 (CONH), 1530, 1510 (C=C)

NMR δ ppm (DMSO):

7.0-7.5 (m, 4H), 7.6-7.8 (m, 3H), 8.36 (d, $J=8.4$ Hz, 1H),
20 8.80 (dd, $J=1.4$ and 8.6 Hz, 1H), 8.83 (s, 1H), 8.95 (dd,
 $J=1.4$ and 1.4 Hz, 1H), 10.4 (bs, 1H).

According to the above described procedure and starting from the appropriate compounds of formula (II) and of formula (III) one can prepare the following compounds as 25 single E- or Z-isomers, as well as their E,Z-mixtures:

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N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide.

$C_{20}H_{18}N_2O_2$ calculated: C 75.45 H 5.70 N 8.80
 found: C 75.35 H 5.65 N 8.75

5 MS m/z 318.

NMR δ ppm (DMSO):

1.77 (m, 4H), 2.55, 2.80 (two m, 4H), 6.78 (d, $J=8.6$ Hz, 1H), 7.11 (m, 1H), 7.34 (m, 2H), 7.64 (m, 2H), 7.80 (d, $J=8.6$ Hz, 1H), 8.31 (s, 1H), 10.18 (s, 1H), 10.3 (bs, 1H).

N-(4'-hydroxyphenyl)- β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-phenyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

15 N-(4'-hydroxyphenyl) β -(3,4-dihydroxy-5,6,7,8-tetra-
hydronaphth-1-yl)- α -cyanoacrylamide;

N-benzyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

N-(4'-hydroxybenzyl) β -(4-hydroxy-5,6,7,8-tetrahydro-
20 naphth-1-yl)- α -cyanoacrylamide;

N-benzyl-6-(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-

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N-(4-Hydroxybenzyl)-

hydronaphth-1-yl)- α -cyanoacrylamide;

REFERENCES AND NOTES

α -cyanoacrylamide; N-(4'-hydroxyphenethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-

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5 naphth-1-yl)- α -cyanoacrylamide;
N-phenethyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(3,4-dihydroxy-5,6,7,8-tetra-
10 hydronaphth-1-yl)- α -cyanoacrylamide;
N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -
cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(4-hydroxy-5,6,7,8-tetrahydro-
15 naphth-2-yl)- α -cyanoacrylamide;
N-benzyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -
cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(4-hydroxy-5,6,7,8-tetrahydro-
naphth-2-yl)- α -cyanoacrylamide;
N-phenethyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -
15 cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-
naphth-2-yl)- α -cyanoacrylamide;

N-phenyl β -(4-quinolyl)- α -cyanoacrylamide.

MS m/z 299.

NMR δ ppm (DMSO):

7.17 (m, 1H), 7.40 (m, 2H), 7.6-8.0 (m, 5H), 8.1-8.4 (m, 2H), 8.95 (s, 1H), 9.09 (d, $J=4.4$ Hz, 1H), 10.65 (s, 1H).

25 N-(4'-hydroxyphenyl) β -(4-quinolyl)- α -cyanoacrylamide;
N-benzyl β -(4-quinolyl)- α -cyanoacrylamide;

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N-(4'-hydroxybenzyl) β -(4-quinolyl)- α -cyanoacrylamide;
 N-phenethyl β -(4-quinolyl)- α -cyanoacrylamide;
 N-(4'-hydroxyphenethyl) β -(4-quinolyl)- α -cyanoacryl-
 amide;
 5 N-(4'-hydroxyphenyl) β -(8-hydroxy-5-quinolyl)- α -cyano-
 acrylamide;
 N-benzyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;
 N-(4'-hydroxybenzyl) β -(8-hydroxy-5-quinolyl)- α -cyano-
 acrylamide;
 10 N-phenethyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;
 N-(4'-hydroxyphenethyl) β -(8-hydroxy-5-quinolyl)- α -
 cyanoacrylamide;
 N-phenyl β -(3-isoquinolyl)- α -cyanoacrylamide.
 15 $C_{19}H_{13}N_3O$ calculated: C 76.24 H 4.38 N 14.04
 found: C 76.15 H 4.27 N 13.95
 MS m/z 299.
 IR cm^{-1} : 3500-3300 (NH); 2215 (CN); 1675, 1605 (CONH);
 1580, 1530 (arom).
 20 N-(4'-hydroxyphenyl) β -(3-isoquinolyl)- α -cyano-
 acrylamide;
 N-benzyl β -(3-isoquinolyl)- α -cyanoacrylamide.
 $C_{20}H_{15}N_3O$ calculated: C 76.66 H 4.83 N 13.41
 found: C 76.51 H 4.75 N 13.36
 MS m/z 313.
 25 IR cm^{-1} : 3500-3300 (NH); 2210 (CN); 1680, 1610 (CONH)

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1585, 1530 (arom).

N-(4'-hydroxybenzyl) β -(3-isoquinolyl)- α -cyanoacryl-
amide;
N-phenethyl β -(3-isoquinolyl)- α -cyanoacrylamide;
5 N-(4'-hydroxyphenethyl) β -(3-isoquinolyl)- α -cyanoacryl-
amide;
N-phenyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(5-isoquinolyl)- α -cyanoacrylamide;
N-benzyl β -(5-isoquinolyl)- α -cyanoacrylamide;
10 N-(4'-hydroxybenzyl) β -(5-isoquinolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(5-isoquinolyl)- α -cyanoacryl-
amide;
N-phenyl β -(3-indolyl)- α -cyanoacrylamide;
15 N-benzyl β -(3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(3-indolyl)- α -cyanoacrylamide;
N-phenyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
20 N-phenyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-phenyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
25 N-phenethyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(3-indolyl)- α -cyanoacrylamide;

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N-(4'-hydroxyphenethyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(5-hydroxy-3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxybenzyl) β -(5-hydroxy-3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxyphenethyl) β -(5-hydroxy-3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxyphenyl) β -(5-carboxy-3-indolyl)- α -cyano-
acrylamide;
10 N-(4'-hydroxybenzyl) β -(5-carboxy-3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxyphenethyl) β -(5-carboxy-3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxyphenyl) β -(5-amino-3-indolyl)- α -cyanoacryl-
15 amide;
N-(4'-hydroxybenzyl) β -(5-amino-3-indolyl)- α -cyanoacryl-
amide;
N-(4'-hydroxyphenethyl) β -(5-amino-3-indolyl)- α -cyano-
acrylamide;
20 N-phenyl β -(5-methoxy-3-indolyl)- α -cyanoacrylamide.
 $C_{19}H_{16}N_3O_2$ calculated: C 71.68 H 5.07 N 13.20
found: C H N
MS m/z 318.
NMR δ ppm (DMSO):
25 3.82 (s, 3H), 7.09 (m, 1H), 6.88 (dd, J=2.4 and 8.8 Hz,
1H), 7.34 (m, 2H), 7.44 (d, J=8.8 Hz, 1H), 7.51 (d, J=8.8
Hz, 1H), 7.67 (m, 2H), 8.45 (s, 1H), 8.55 (s, 1H), 10.1

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(bs, 1H).

N-benzyl β -(5-methoxy-3-indolyl)- α -cyanoacrylamide.

$C_{20}H_{18}N_3O_2$ calculated: C 72.27 H 5.96 N 12.64

found: C 72.15 H 5.35 N 12.63

5 MS m/z 332.

NMR δ ppm (DMSO):

3.80 (s, 3H), 4.42 (d, $J=5.9$ Hz, 2H), 6.87 (dd, $J=2.2$ and 8.8 Hz, 1H), 7.2-7.5 (m, 7H), 8.39 (s, 1H), 8.47 (s, 1H), 8.75 (t, $J=5.9$ Hz, 1H), 12.2 (bs, 1H).

10 N-(3-pyridyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

N-(3-pyridyl) β -(3-indolyl)- α -cyanoacrylamide;

N-(3-pyridyl) β -(5-methoxy-3-indolyl)- α -cyanoacrylamide;

N-(3-pyridyl) β -(4-quinolyl)- α -cyanoacrylamide;

15 N-(3-pyridylmethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;

N-(3-pyridylmethyl) β -(3-indolyl)- α -cyanoacrylamide;

N-(3-pyridylmethyl) β -(5-methoxy-3-indolyl)- α -cyano-acrylamide.

20 $C_{19}H_{16}N_4O_2$ calculated: C 68.66 H 4.85 N 16.86

found: C 68.53 H 4.76 N 16.73

MS m/z 332.

NMR δ ppm (DMSO):

3.80 (s, 3H), 4.43 (d, $J=5.9$ Hz, 2H), 6.87 (dd, $J=2.4$ and

25 8.8 Hz, 1H), 7.35 (ddd, $J=1.9$ and 4.8 and 7.9 Hz, 1H),

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7.42 (m, 2H), 7.72 (ddd, $J=7.9$ and 1.8 and 2.3 Hz, 1H),
 8.39, 8.46 (two s, 2H), 8.45 (dd, $J=1.8$ and 4.8 Hz, 1H),
 8.54 (dd, $J=2.3$ and 1.9 Hz, 1H), 8.80 (t, $J=6.0$ Hz, 1H),
 12.2 (bs, 1H).

5 N-(3-pyridylmethyl) β -(4-quinolyl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-
naphth-1-yl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(5-methoxy-3-indolyl)- α -cyano-
10 acrylamide;
N-(2-pyridylmethyl) β -(4-quinolyl)- α -cyanoacrylamide.

Example 2

N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide.

15 To a stirred solution of N-phenyl β -(4-methoxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide (3.324 g, 0.01 mol) in anhydrous dichloromethane (100 ml) was added at -78°C under nitrogen, over a period of 20 min, a 1 M boron tribromide solution in dichloromethane (30 ml, 0.030 mol).
20 The resulting mixture was stirred for another 1 h at -78°C and then allowed to warm up to room temperature. After stirring for 1.5 h at room temperature the mixture was cooled to -10°C and then quenched by dropwise addition of water (100 ml) over a 10-min period. After addition of
25 ethyl acetate (100 ml) the organic layer was separated,

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washed with water, dried over Na_2SO_4 and evaporated under vacuum to dryness. The residue was crystallized from ethanol thus giving pure title compound in 65% yield (2.070 g).

MS m/z 318.

IR cm^{-1} : 3100-3500 (NH, OH), 2210 (CN), 1685, 1610 (CONH), 1585, 1560, 1520 (C=C).

10 Following the above described procedure and starting from a phenolic methyl ether of formula (I), which may be obtained according to the procedure described in example 1, the corresponding phenolic compound of formula (I) may be obtained.

15 Example 3

N-phenyl β -(5-amino-3-indolyl)- α -cyanoacrylamide.

To a solution of N-phenyl β -(5-nitro-3-indolyl)- α -cyanoacrylamide (3.324 g, 0.010 mol) in anhydrous ethanol (200 ml) was added palladium on charcoal (0.200 g) and the mixture was hydrogenated at room temperature and atmospheric pressure until 3 equivalent of hydrogen has been taken up. The hydrogen uptake was graphed as function of time. The catalyst was filtered and the solution concentrated under vacuum until crystallization began. The mixture was cooled to 0-5°C, filtered, the residue washed

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with ice-cooled ethanol and dried under vacuum. Thus almost pure title compound was obtained in about 80% yield (2.416 g). An analytical pure sample was obtained by crystallization from ethanol.

MS m/z 302.

IR cm^{-1} : 3400, 3300 (NH), 2220 (CN), 1680, 1620 (CONH),
1590, 1510 (C=C).

10 Proceeding analogously and starting from a nitro compound of formula (I), which may be obtained according to the procedure described in Example 1, the corresponding amino compound of formula (I) can be obtained.

Example 4

15 N-phenyl β -(4-acetoxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide.

To a cooled solution of N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide (3.184 g, 0.010 mol) in dry pyridine (5 ml) was added acetic anhydride (2.040 g, 0.020 mol) and the mixture maintained at 0-5°C overnight. Thereupon the mixture was concentrated under vacuum, the residue dissolved in dichloromethane, the organic layer washed with water and then evaporated under reduced pressure. The crude product was crystallized from chloroform/methanol to yield pure title compound in about

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80% yield.

$C_{22}H_{20}N_2O_3$ calculated: C 73.32 H 5.59 N 7.77

found: C 73.25 H 5.45 N 7.65

MS m/z 360.

5 IR cm^{-1} : 3300 (NH), 2200 (CN), 1755 (ester), 1690 (amide), 1620 (amide).

According to this procedure the phenols of formula (I) obtained in Example 1 can be transformed into the corresponding acetoxy derivatives of formula (I).

10 Example 5

1,4-dihydroxy-5,6,7,8-tetrahydro-2-naphthaldehyde.

To a solution of 1,4-dihydroxy-5,6,7,8-tetrahydro-naphthalene (1.640 g, 0.010 mol) in dichloromethane (50 ml) was added titanium tetrachloride (5.69 g, 0.03 mol). Then 15 1,1-dichlorodimethyl ether (1.73 g, 0.015 mol) was added dropwise under vigorous stirring and the reaction mixture stirred for another 3 h at room temperature. Finally 5% hydrochloric acid (10 ml) was added under ice-cooling. The organic phase was separated and the residual aqueous phase 20 repeatedly extracted with ether. The combined organic phases are washed with saturated saline solution, dried over sodium sulfate and evaporated under vacuum. The residue was crystallized from benzene or alternatively submitted to flash chromatography on silica gel with 25 benzene/ethylacetate 85:15 to afford pure title compound in

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about 60% yield (1.080 g), mp 145°C.

MS m/z 180.

NMR δ ppm: 10.4 (bs, OH), 9.7 (s, CHO), 9.1 (bs, OH),
6.9 (s, H arom), 2.8 (m, 5-CH₂, 8-CH₂), 1.9
5 (m, 6-CH₂, 7-CH₂).

Example 6

5-nitro-3-indolealdehyde.

A mixture of N-methylformanilide (1.76 g, 0.013 mol) and phosphorous oxychloride (1.99 g, 0.013 mol) was stirred for
10 15 min at 20-25°C under nitrogen.

Then a solution of 5-nitroindole (1.62 g, 0.01 mol) in 1,2-dichloroethane (50 ml) was added and the mixture heated to reflux for 3 h. After cooling the mixture was poured onto iced water, the precipitate filtered off and washed with
15 water. Thereupon the residue was chromatographed over silica gel using benzene/ethylacetate as eluant. Thus pure title compound was obtained in 80% yield (1.52 g).

$C_9H_6N_2O_3$ calculated: C 56.85 H 3.18 N 14.73
found: C 56.79 H 3.01 N 14.51

20 MS m/z 190.

IR cm^{-1} : 3140, 3090 (NH), 1650 (CO), 1511, 1345 (NO₂).

Example 7

N-benzyl α -cyanoacetamide.

To benzylamine (1.07 g, 0.01 mol) was added methyl

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cyanoacetate (0.99 g, 0.01 mol) and the mixture was heated for 16 h at 100°C without condenser to allow evaporation of the methanol formed. Cooling gave a dark red solid which was triturated with ethanol, filtered and recrystallized 5 from ethanol to give pure title compound in about 40% yield (0.70 g). mp 123-4°C.

MS m/z 174.

According to the above described procedure and starting from the appropriate compounds of formula (V) and of 10 formula (VI) one can prepare the corresponding compounds of formula (III).

Example 8

Tablets each weighing 0.150 g and containing 25 mg of the active substance, can be manufactured as follows:

15 composition (for 10,000 tablets):

N-phenyl β -(8-hydroxy-5-quinolyl)-	
α -cyanoacrylamide	250 g
Lactose	800 g
Corn starch	415 g
20 Talc powder	30 g
Magnesium stearate	5 g

N-phenyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide, the lactose and half the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm mesh size.

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Corn starch (10 g) is suspended in warm water (90 ml) and the resulting paste is used to granulate the powder. The granulate is dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and 5 magnesium stearate are added, carefully mixed and processed into tablets.

Example 9

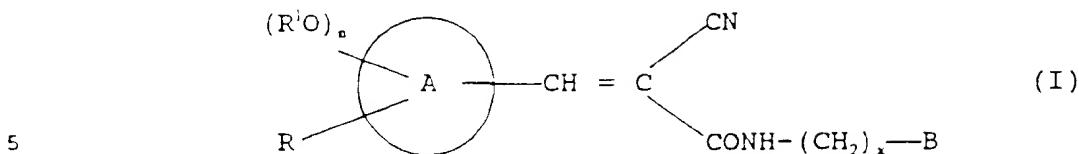
Capsules, each dosed at 0.200 g and containing 20 mg of the active substance can be prepared.

10 Composition for 500 capsules:

N-benzyl β -(5-methoxy-3-indolyl)-		
α -cyanoacrylamide		10 g
Lactose		80 g
Corn starch		5 g
15 Magnesium stearate		5 g

This formulation is encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

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CLAIMS1. A compound of formula (I)

wherein

A is a bicyclic ring chosen from naphthalene, tetrahydronaphthalene, quinoline, isoquinoline and indole.

10 B is a R² substituted benzene ring or an unsubstituted pyridine or thiophene ring;

R is hydrogen, C₁-C₆ alkyl, halogen, nitro, cyano, carboxy or a group NR³R⁴ wherein each of R³ and R⁴ is independently hydrogen or C₁-C₆ alkyl;

15 R¹ is hydrogen, C₁-C₆ alkyl or C₁-C₆ alkanoyl;

R² is hydrogen, C₁-C₆ alkyl, halogen, nitro, cyano, carboxy, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkanoyloxy or a group NR³R⁴ wherein R³ and R⁴ are as defined above;

20 n is zero or an integer of 1 to 2;

x is zero or an integer of 1 to 5;

and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I), according to claim 1, wherein

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A is tetrahydronaphthalene, quinoline, isoguinoline and indole;

B is R^2 substituted benzene or unsubstituted pyridine;

5 R is hydrogen or halogen with the exception of
indole derivatives where R can also be carboxy
or amino;

R¹ is hydrogen or methyl;

R^2 is hydrogen, halogen, cyano, hydroxy, carboxy or amino;

10 amino;

n is 0, 1 or 2; and

x is 0, 1, 2 or 3;

and the pharmaceutically acceptable salts thereof.

3. A compound of formula (I) according to claim 2,
wherein

15 wherein

A is tetrahydronaphthalene, quinoline, isoquinoline and indole;

B is R² substituted benzene or an unsubstituted pyridine;

20 R is hydrogen with the exception of indole derivatives where R can also be carboxy or amino;

R¹ is hydrogen or methyl;

R^2 is hydrogen or hydroxy;

25 n is 0 or 1 and

x is 0, 1 or 2,

and the pharmaceutically acceptable salts thereof.

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4. A compound selected from the group consisting of the following compounds, the compound being the Z-isomer or E-isomers, or a mixture of the Z- and E-isomers:

5 N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
10 N-(4'-hydroxyphenyl)- β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
15 N-phenyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
20 N-(4'-hydroxyphenyl) β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
25 N-benzyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
30 N-(4'-hydroxybenzyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
35 N-benzyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
40 N-(4'-hydroxybenzyl) β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
45 N-phenethyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
50 N-(4'-hydroxyphenethyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
55 N-phenethyl β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;
60 N-(4'-hydroxyphenethyl) β -(3,4-dihydroxy-5,6,7,8-tetrahydronaphth-1-yl)- α -cyanoacrylamide;

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N-phenyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -cyanoacrylamide;
5 N-benzyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -cyanoacrylamide;
N-phenethyl β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -cyanoacrylamide;
10 N-(4'-hydroxyphenethyl) β -(4-hydroxy-5,6,7,8-tetrahydronaphth-2-yl)- α -cyanoacrylamide;
N-phenyl β -(4-quinolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(4-quinolyl)- α -cyano-
15 acrylamide;
N-benzyl β -(4-quinolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(4-quinolyl)- α -cyano-
acrylamide;
N-phenethyl β -(4-quinolyl)- α -cyanoacrylamide;
20 N-(4'-hydroxyphenethyl) β -(4-quinolyl)- α -cyano-
acrylamide;
N-phenyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(8-hydroxy-5-quinolyl)- α -
25 cyanoacrylamide;
N-benzyl β -(8-hydroxy-5-quinolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(8-hydroxy-5-quinolyl)- α -
cyanoacrylamide;
N-phenethyl β -(8-hydroxy-5-quinolyl)- α -cyano-

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acrylamide;
N-(4'-hydroxyphenethyl) β -(8-hydroxy-5-quinolyl)- α -
cyanoacrylamide;
N-phenyl β -(3-isoquinolyl)- α -cyanoacrylamide;
5 N-(4'-hydroxyphenyl) β -(3-isoquinolyl)- α -cyano-
acrylamide;
N-benzyl β -(3-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(3-isoquinolyl)- α -cyano-
acrylamide;
N-phenethyl β -(3-isoquinolyl)- α -cyanoacrylamide;
10 N-(4'-hydroxyphenethyl) β -(3-isoquinolyl)- α -cyano-
acrylamide;
N-phenyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4-hydroxyphenyl) β -(5-isoquinolyl)- α -cyano-
15 acrylamide;
N-benzyl β -(5-isoquinolyl)- α -cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(5-isoquinolyl)- α -cyano-
acrylamide;
N-phenethyl β -(5-isoquinolyl)- α -cyanoacrylamide;
20 N-(4'-hydroxyphenethyl) β -(5-isoquinolyl)- α -cyano-
acrylamide;
N-phenyl β -(3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(3-indolyl)- α -cyanoacrylamide;
25 N-phenyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-hydroxy-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-hydroxy-3-indolyl)- α -cyano-
acrylamide;

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N-phenyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-carboxy-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-carboxy-3-indolyl)- α -cyano-
acrylamide;
5 N-phenyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-benzyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-phenethyl β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(3-indolyl)- α -cyano-
acrylamide;
10 N-(4'-hydroxybenzyl) β -(3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxyphenethyl) β -(3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxyphenyl) β -(5-hydroxy-3-indolyl)- α -
15 cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(5-hydroxy-3-indolyl)- α -
cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(5-hydroxy-3-indolyl)- α -
cyanoacrylamide;
20 N-(4'-hydroxyphenyl) β -(5-carboxy-3-indolyl)- α -
cyanoacrylamide;
N-(4'-hydroxybenzyl) β -(5-carboxy-3-indolyl)- α -
cyanoacrylamide;
N-(4'-hydroxyphenethyl) β -(5-carboxy-3-indolyl)- α -
25 cyanoacrylamide;
N-(4'-hydroxyphenyl) β -(5-amino-3-indolyl)- α -cyano-
acrylamide;
N-(4'-hydroxybenzyl) β -(5-amino-3-indolyl)- α -cyano-

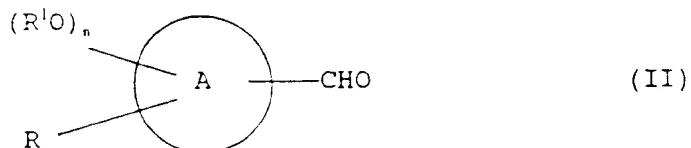
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acrylamide;
N-(4'-hydroxyphenethyl) β -(5-amino-3-indolyl)- α -cyanoacrylamide;
N-phenyl β -(5-methoxy-3-indolyl)- α -cyanoacrylamide;
5 N-benzyl β -(5-methoxy-3-indolyl)- α -cyanoacrylamide;
N-(3-pyridyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;
N-(3-pyridyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(3-pyridyl) β -(5-methoxy-3-indolyl)- α -cyano-10
acrylamide;
N-(3-pyridyl) β -(4-quinolyl)- α -cyanoacrylamide;
N-(3-pyridylmethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-naphth-1-yl)- α -cyanoacrylamide;
N-(3-pyridylmethyl) β -(3-indolyl)- α -cyanoacrylamide;
15 N-(3-pyridylmethyl) β -(5-methoxy-3-indolyl)- α -cyano-
acrylamide;
N-(3-pyridylmethyl) β -(4-quinolyl)- α -cyano-
acrylamide;
N-(2-pyridylmethyl) β -(4-hydroxy-5,6,7,8-tetrahydro-20
naphth-1-yl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(3-indolyl)- α -cyanoacrylamide;
N-(2-pyridylmethyl) β -(5-methoxy-3-indolyl)- α -cyano-
acrylamide;
N-(2-pyridylmethyl) β -(4-quinolyl)- α -cyano-25
acrylamide, and, when appropriate, the
pharmaceutically acceptable salts thereof.

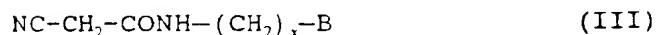
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5. A process for preparing a compound of formula (I), according to claim 1, comprising the condensation of an aldehyde of formula (II)

5



wherein A, R, R¹ and n are as defined in claim 1, with a compound of formula (III)



10 wherein R² and x are as defined in claim 1, and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof, and/or, if 15 desired, converting a salt into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I) into the single isomers.

20 6. A pharmaceutical composition comprising a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

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7. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as a tyrosine kinase inhibitor.
- 5 8. A compound of formula (I) as defined in claim 7, or a pharmaceutically acceptable salt thereof, for use as anticancer agent or in the treatment of leukemia, psoriasis or atheromatous plaque.
- 10 9. A compound of formula (I) as defined in claim 7, or a pharmaceutically acceptable salt thereof, for use as immunosuppressant agent.
10. Use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use as a tyrosine kinase inhibitor.
- 15 11. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 9, in the preparation of a medicament for use as anticancer agent or in the treatment of leukemia, psoriasis or atheromatous plaque.
- 20 12. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 9, in the preparation of a medicament for use as immunosuppressant agent.

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13. A compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, for use in a method of treatment of the human or animal body by therapy.

5 14. Products containing a compound of formula (I) or a
pharmaceutically acceptable salt thereof, according to
claim 1 and an antitumor agent as a combined
preparation for simultaneous, separate or sequential
use in anticancer therapy.

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.
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^A CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D215/26 A61K31/33 C07D215/14 C07D217/16 C07D209/18
 C07D401/12 C07C255/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 537 742 (MITSUBISHI KASEI CORPORATION) 21 April 1993 * complete document * ---	1,7
Y	WO,A,91 13055 (FARMITALIA CARLO ERBA S.R.L.) 5 September 1991 * complete document * ---	1,7
X	WO,A,91 16305 (RORER INTERNATIONAL, INC.) 31 October 1991 * claim 4 * ---	1,7
A	GB,A,2 240 104 (FARMITALIA CARLO ERBA S.R.L.) 24 July 1991 see claims ---	1,7 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

17 May 1995

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Name and mailing address of the ISA

 European Patent Office, P.O. 5818 Patentzaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
 Fax (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 95/00758

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.
Category	Reference of document, with indication, where appropriate, of the relevant passages	
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